REMARKS

Upon entry of the Amendment, Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49, and 52-53 are pending in the application. Claims 1-14, 18-20, 25-30, 32-33, 36-39, 46-47, 50-51 were previously canceled without prejudice. Claims 15, 21, 42, 48, 52, and 53 have been amended. No new matter has been added. Support for the amendments to the claims can be found in the claims and throughout the specification as originally filed.

Amendments to and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of: (a) the previous rejection of the claims under 35 USC §112, 1st paragraph, and (b) 35 USC §102(b)/(e) as anticipated by Salfeld.

Rejections Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, and 52-53 under 35 U.S.C. 112, second paragraph, contending they are indefinite for reciting "a low dose of 0.01-0.1 mg/kg," contending that the dosage frequency is unclear.

Not in acquiescence of the rejection but in order to expedite allowance of the claims, Applicants respectfully submit that the claims have been amended to recite that the low dose was administered by injection . . .at a frequency of not more than once per week. Applicants respectfully submit that support for the amendment is found in Example 1B, beginning on page 27. Applicants therefore request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph

Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, and 52-53 under 35 U.S.C. 112, first paragraph, contending that the specification is not enabling for

treating arthritis with 0.01- 0.1 mg/kg anti-TNFα antibody. Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Contrary to the Examiner's contention that the data and the Figures do not support an effect using a 0.01 mg/kg dose of anti-TNFα antibody, Applicants respectfully submit that Figure 4 indicates that a 0.01 mg/kg dose of Adalimumab resulted in an arthritic score as low as about 1.0 in at least one mouse (see low point of standard deviation mark) compared to the lowest arthritic score of about 2.25 in a control mouse. Similarly, a 0.01 mg/kg dose of Infliximab resulted in at least one mouse that had an arthritic score of about 1.75 compared to the lowest arthritic score in a control mouse of about 2.25. Applicants respectfully submit that these results indicate efficacy of both Adalimumab and Infliximab at a dosage of 0.01 mg/kg. Applicants respectfully submit that the effect on arthritic score need not affect each and every mouse in a study in order for the dose to be enabled and that it is particularly significant that at least one mouse in the study had an arthritic score of about 1.0, which is substantially and significantly lower than 2.25, the lowest arthritic score for a control mouse.

The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. MPEP at 2164.08(b). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

Section 112 does not require that Applicants describe every equivalent within the scope of the claims so long as the specification provides sufficient teachings for a person of skill in the art to identify additional equivalents without undue experimentation. *In re Wands*, 8 USPQ2d 1400-1407, 1404 (CAFC, 1988). The fact that some experimentation is required does not preclude a finding of enablement. *See, e.g., In re Angstadt*, 537 F.2d 498, 503 and *Amgen Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1213 (CAFC 1991). Moreover, "as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement

of §112 is satisfied." *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added).

The example provided on page 27 uses the concentration of 0.01 mg/kg and demonstrates a significant effect on certain mice. A skilled artisan would determine from the standard deviation that the 0.01 mg/kg dose is likely to be effective for some patients. Even if, *arguendo*, some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be "undue" for a skilled artisan, since drug dosages have to be optimized for each patient regardless. Applicants therefore respectfully submit that there is a reasonable correlation between the scope of the claims and the scope of enablement and that therefore the dosage range including 0.01 mg/kg dose is enabled, even though for certain mice the response was not optimal. Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

Rejection of Claims Under 35 U.S.C. § 102(b)

The Examiner rejected claims 15-17 and 21-24 under 35 U.S.C. § 102(b) as being anticipated by Stephens *et al.* (Antibody Therapeutic (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, Fla.) (hereinafter "Stephens"). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Contrary to the Examiner's contention, Applicants respectfully submit that although Stephens mentions a 0.01 mg/kg dose in the study and provides a general statement that "[a]ll patients who receive CDP571 scored a reduction in pain scale by week 1", all discussion of the data in support of that general statement are for 0.1mg/kg and 10 mg/kg. Stephens shows no data on the 0.01 mg/kg dose and does not discuss the effectiveness of this dose at all, nor is it tested further in subsequent infusions, suggesting that it was ineffective in their study. Applicants respectfully submit that a skilled artisan would no doubt assume that this dose was not studied further because it was not effective. In addition, there was no indication or evidence that the 0.01 mg/kg dose "treated arthritis" as required by Applicants' claims.

In addition, Stephens discloses only infusions of CDP571, not injections of an anti-TNFα antibody in a 0.01 mg/kg dose, which is required by Applicants' claims as amended.

Since Stephens does not identically disclose every element of Applicants' claims as amended, Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 102(b).

Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49 under 35 U.S.C. § 103(a) as being obvious over Stephens *et al.* (Antibody Therapeutic (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, Fla.) in view of Salfeld et al. (U.S. Patent No. 6,258,562; hereinafter referred to as "Salfeld") and den Broeder *et al.* (Rheumatology 2002, 41(6):638-42; hereinafter "den Broeder"). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03). The claimed methods are unique in that they embody Applicants' unexpected discovery that a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody can be effective in treating arthritis and alleviating symptoms associated with arthritis.

Stephens, as discussed above, does not teach an injection regime for an anti-TNFα antibody as a treatment for arthritis and provides no evidence or suggestion that 0.01 mg/kg dosage would be effective at treating arthritis. Since Stephens provides no data that suggests a 0.01 mg/kg dose would treat arthritis, or that it should be injected, a skilled artisan, using

Stephens as a guide, would not be motivated to use that dose to treat arthritis. Thus, Stephens teaches away from the claimed invention of treating arthritis by administering a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody. Specifically, one of ordinary skill in the art would not have been motivated, based on the disclosure of Stephens, to treat arthritis with a low dose of 0.01-0.1 mg/kg, since Stephens provides no teaching that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis and, moreover, teaches that a low dose of the antibody mounts an immune response and is cleared from the patient's system to a greater extent than a higher dose, *e.g.*, 10 mg/kg, of CDP571.

Salfeld fails to make up for this deficiency. Salfeld provides general guidance with regard to normally prescribed dosing but fails to teach or suggest methods that use a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody. In particular, as acknowledged by the Examiner, Salfeld teaches that a therapeutically effective dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. In addition, Salfeld disclosed only treatment of rheumatoid arthritis using a range of 1.5 μg/g to 30 μg/g, in other words, 1.5 mg/kg to 30 mg/kg (see Example 4, part D, section III, Table 15). Salfeld thus fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg as an effective treatment for arthritis with sufficient specificity to constitute an anticipation of the pending claims, and as such does not provide a motivation to do so. Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of Salfeld, because Salfeld already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg. Further, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. §2131.03). In the present case, while the Salfeld discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of Salfeld.

Den Broeder also fails to make up for the deficiencies of Stephens and Salfeld. Den Broeder discloses a dose of 2.5 mg/kg delivered intravenously every 2-4 weeks. It is inappropriate for the Examiner to extrapolate from that disclosure by calculating the dosage on

a weekly basis so that it falls within the Applicants dose range of 0.01 to 1.0 mg/kg. At no time does DenBroeder inject less than a 0.25 mg/kg dose, which is well above and outside Applicants' dose range required in the claims as amended.

Den Broeder reports on a clinical, dose titration study involving patients that had ongoing, successful treatment of rheumatoid arthritis with D2E7 for at least a year prior to the dose titration study at a fixed dose of 3.0 mg/kg, and at an interval of every 2 or 4 weeks. These patients were subjected to a step-wise reduction in dose at regular dosing intervals (every 2 or 4 weeks), *e.g.*, from 3.0 to 1.0, 0.5 and eventually to 0.25 mg/kg. Den Broeder reports the results of this study, wherein "six out of 21 patients were placed back on the original dose of 3.0 mg/kg after flaring on 1.0 mg/kg, whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg." Further, den Broeder discloses that, based on these results, "the median of the calculated weekly dose of anti-TNFα administered to these patients was ... 32.5 mg week" (page 641, second paragraph), which is equivalent to 0.36 mg/kg per week for a 90 kg person. Thus, den Broeder fails to teach or suggest a method of treating arthritis by administering a dose lower than 0.25 mg/kg, let alone a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody, as required by the instant claims.

Moreover, one of skill in the art would not have been motivated, based on the disclosure of den Broeder, to practice the claimed invention of treating arthritis at a low dose of 0.01-0.1 mg/kg. Notably, den Broeder teaches that "[a] drawback of step-down dose titration is the inevitable disease flare in the titration phase" and note that "eighteen out of 21 patients experienced a flair of the disease" (page 641, last paragraph; emphasis added). Indeed, only three out of 21 patients reached the dose of 0.25 mg/kg, while the remaining 18 patients experienced a flair in disease at even higher doses. Thus, den Broeder teaches away from the claimed low dose of 0.01-0.1 mg/kg in that it teaches that even at a dose of 0.25 mg/kg (or greater), 18 out of the 21 patients treated experienced a flair in disease. One of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder, to treat with doses lower than 0.25 mg/kg, since only a small percentage of patients (i.e., 3 out of 21) were observed to reach the dose of 0.25 mg/kg before exhibiting a flare in disease.

In view of all of the foregoing, it is evident that Stephens in view of the teachings of Salfeld and den Broeder fail to render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Provisional Rejection Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, and 52-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (a) claims 1-7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69, and 70 of US Patent No. 6,509,015; (b) claims 1-10 of US Patent No. 7,223,394 (hereinafter the '394 patent); and claims 15-17 and 19 of co-pending U.S. Application No. 11/233,252 (hereinafter referred to as "the '252 application"), each in view of Salfeld and den Broeder.

Regarding the '252 application, Applicants respectfully acknowledge the provisional rejection of these claims and request that the rejection be held in abeyance until allowance of the claims at which time an analysis of the double patenting rejection will be conducted to determine the appropriateness of a terminal disclaimer.

Applicants respectfully traverse the aforementioned obviousness-type double patenting rejection over the '015 and '294 patents on the grounds that the claimed low dose methods would not have been obvious to one of ordinary skill in the art based on the claims of the '015 patent or the '394 patent.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (M.P.E.P. § 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would

have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03).

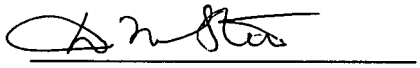
The claimed methods are unique in that they embody Applicants' unexpected discovery that low doses, *e.g.*, 0.01-0.1 mg/kg, of anti-TNFα antibodies can be effective in treating arthritis and alleviating symptoms associated with arthritis. Applicants teach in the specification various benefits associated with administering low doses of the anti-TNFα antibodies, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification). Applicants also teach in the specification that low doses of an anti-TNFα antibody may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification). In contrast, the claims of the '015 patent are directed to methods for treating rheumatoid arthritis by administering a human anti-TNFα antibody. The '015 and '394 patents fail to teach or suggest a low dose of 0.01 – 0.1 mg/kg of a human anti-TNFα antibody.

Accordingly, Applicants respectfully request that the rejection of claims under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (508)688-8048.

Respectfully submitted,



Diana M. Steel, D. Phil.
Attorney for Applicants
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605-4314

Date: November 8, 2007
Registration No. 43,153
Tel. No. (508) 688-8048
Fax No. (508) 688-8110